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Leukemogenic Risk of Hydroxyurea Therapy in Polycythemia Vera, Essential Thrombocythemia, and Myeloid Metaplasia With Myelofibrosis

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In polycythemia vera (PV), treatment with chlorambucil and radioactive phosphorus (p32) increases the risk of leukemic transformation from 1% to 13–14%. This risk has been estimated to be 1–5.9% with hydroxyurea (HU) therapy. When compared with historical controls, the risk with use of HU does not appear to be statistically significant. The leukemogenic risk of HU therapy in essential thrombocytosis (ET) and in myelofibrosis with myeloid metaplasia (MMM) is unknown. HU remains the main myelotoxic agent in the treatment of PV, ET, and MMM. We studied 64 patients with these three disorders, seen at our institution during 1993–1995. The patients were studied for their clinical characteristics at diagnosis, therapies received, and development of myelodysplasia or acute leukemia (MDS/AL). Forty-two had PV, 15 ET, and 6 MMM, and 1 had an unclassified myeloproliferative disorder. Of the 42 patients with PV, 18 were treated with phlebotomy alone, 16 with HU alone, 2 with p32, 2 with multiple myelotoxic agents, and 2 with interferon-α (IFN-α). Two patients from the phlebotomy-treated group, one from the HU-treated group, and 1 from the multiple myelotoxic agent-treated group developed MDS/AL. In the larger group, 11 received no treatment or aspirin alone, 18 were treated with phlebotomy alone, 25 with HU, 5 with multiple myelotoxic agents, 2 with p32, 2 with IFN-α, and 1 with melphalan. Study of the entire group of 64 patients showed that only one additional patient (total of 5 out of 64) developed MDS/AL. This patient had been treated with HU alone. Statistical analysis did not show any association between clinical characteristics at diagnosis, or HU therapy, and development of MDS/AL ($P = 0.5$). Thus, our data provide no evidence suggestive of increased risk of transformation to MDS/AL with HU therapy in PV, ET, and MMM. Larger, prospective studies are needed to study this issue further. © 1996 Wiley-Liss, Inc.

Key words: polycythemia vera, essential thrombocytosis, myelofibrosis with myeloid metaplasia, hydroxyurea

INTRODUCTION

About 1% of the patients with polycythemia vera (PV) treated with phlebotomy alone progress to acute myeloid leukemia [1–3]. If these patients are also treated with radioactive phosphorus (p32) or alkylating agents, the risk of acute leukemia increases to 13–14% [4]. Patients treated with hydroxyurea (HU) have been reported to have about 5.9% incidence of developing acute leukemia, a risk that has not been found to be statistically significant when compared to historical controls [5]. Others have reported that risk of leukemic transformation with HU is small [6–8], but these studies are uncontrolled.

Even though the standard treatment of PV is phlebotomy, myelosuppressive therapy becomes necessary in more than one-half of patients with this diagnosis [9]. Since 1981, when the Polycythemia Vera Study Group (PVSG) reported on the leukemogenic effects of p32 and alkylating agents in PV, HU has been the major

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myelosuppressive agent in use [10]. Recently, interferon-α (IFN-α) has been tried in PV with reports of initial success [11,12]. Because IFN-α is available only in injectable form and has significant systemic side effects, its wider use has been limited. Also, the long-term toxicity of IFN-α therapy in PV is unknown.

The treatment options in essential thrombocythemia (ET) include antiplatelet agents, anagrelide, IFN-α, and myelosuppressive agents. In myeloid metaplasia with myelofibrosis (MMM), splenectomy is frequently necessary. In both disorders, HU is commonly used and is considered the myelosuppressive agent of choice [13,14]. Acute leukemia is seen in 3–5% of the patients with ET, but this risk appears higher in patients with MMM [13–15]. Even though the leukemic transformation has been seen primarily in patients treated with myelosuppressive agents, including HU, the role of myelosuppressive agents regarding this complication remains unclear.

Therefore, at present, HU remains the preferred myelosuppressive agent in the treatment of PV, ET, and MMM. There are theoretical reasons to suspect that it could be leukemogenic [16]. The clinical data available so far fail to confirm or rule out a leukemogenic potential of this agent. We reviewed our own experience over the last 2 years to determine the incidence of acute leukemia and myelodysplasia in patients with PV, ET, and MMM who were treated with hydroxyurea.

MATERIALS AND METHODS

All patients seen at Loyola University Medical Center with the diagnosis of PV between July 1993 and February 1995 were included. The diagnostic criteria used were those published by Berlin [17]. Patients were studied for their initial presenting features (e.g., age, sex, presence of splenomegaly, initial hemogram, vitamin B_{12} level, neutrophil alkaline phosphatase level, and red cell mass), type of therapy received, duration of follow-up, and development of myelodysplasia or acute leukemia. Myelosuppressive therapy was quantified as follows: hydroxyurea dose in gram-years (g-yr), where 1 g-yr = 1 g/day for 1 year, and melphalan in total mg/month. Patients who received more than one myelosuppressive agent were included in the multiple therapy group.

In addition to the PV patients, we saw 22 patients with ET and MMM. These patients were added to the PV group, and the same study parameters were analyzed for the larger group.

All data were analyzed using parametric methods including Student's *t*-test for continuous data and the Fisher's exact test for the frequency data. Two-tailed probabilities of <0.05 were considered statistically significant.

RESULTS

Polycythemia Vera Group

A total of 42 patients with PV were seen during the study period. Twenty-two were males, and median age at diagnosis was 64 years. At diagnosis, the mean hemoglobin level was 16.9 g/dl (range 13.9–23), mean white blood cell (WBC) count 13.9×10^9/L (range 5–32.2), platelet count 701×10^9/L (113–1594), B_{12} level 828 pg/ml (221–1583), and LAP score 158 (17–285) (Table I). Eighteen patients were treated with phlebotomy alone, with the other 24 requiring additional therapy as follows: HU, 16; p32, 2; more than one myelotoxic agent, 4 (HU and busulfan, HU and chlorambucil, p32 and HU, chlorambucil plus p32 plus HU), and IFN-α 2. The dose of HU varied between 0.5 g-yr to 6 g-yr (median 1.5 g-yr). Patients had been followed for 1.5–20 years from the time of diagnosis, with a median follow-up of 5.5 years. The study represents 126 patient-years of HU therapy plus 25 patient years of post-HU therapy observation period.

Two patients from the phlebotomy-treated group, one from the HU-treated group, and one who received multiple myelosuppressive therapies, developed myelodysplastic syndrome (MDS) or acute leukemia (AL). In the phlebotomy-treated group, the leukemic/preleukemic event occurred at 70 and 98 months after diagnosis, respectively. In the HU-treated group, it occurred 52 months after diagnosis, when the patient had received HU for 18 months. The fourth patient had been treated with p32 once and with chlorambucil (2 mg/day) for 4 years and had been receiving HU for 50 months, when she transformed to MDS (refractory anemia with excess blasts). This occurred 228 months after her diagnosis. Three of these patients died within 3 months of diagnosis; the fourth patient, with a diagnosis of refractory anemia with excess blasts, is alive at 15 months.

There was no difference in the incidence of leukemia transformation based on the therapy received in these patients ($P = 0.54$) (Table II). In particular, the use of HU was not associated with an increased risk of MDS and AL.

Polycythemia Vera, Essential Thrombocythemia, and Myeloid Metaplasia With Myelofibrosis Group

In this larger group, there were 22 additional patients: 15 with ET, 6 with MMM, and 1 with an unclassified myeloproliferative disorder. There were 34 males, and the median age at diagnosis was 63 years. Other clinical data obtained at diagnosis are listed in Table I. Eleven patients received either no treatment or only oral aspirin. Eighteen were treated with phlebotomy alone, 25 with HU, 1 with melphalan, 2 with p32, 5 with more than 1 myelosuppressive agent, and 2 with IFN-α. The cumulative dose of HU varied between 0.25 to 6 g-yr (median

TABLE I. Clinical Characteristics of Patients at Diagnosis*

Variable	Polycythemia vera	Polycythemia vera, myeloid metaplasia with myelofibrosis, and essential thrombocytosis
No. of patients	42	64
Median age (yr)	64	63
Male:female	22:20	34:30
Hemoglobin (g/dl)	16.9 (13.9–23) ± 2.9	15.3 (11.1–23) ± 3.5
WBC count ($\times 10^9$/L)	13.9 (5–32.2) ± 6.1	12.9 (4.1–28.4) ± 6.3
Platelet count ($\times 10^9$/L)	701 (113–1,594) ± 362	721 (113–1,594) ± 360
B_{12} level	828 (221–1,583) ± 433	859 (221–1,583) ± 437
NAP score	158 (17–285) ± 89	143 (17–285) ± 94

NAP, neutrophil alkaline phosphatase.
*Hemogram values, B_{12} levels, and NAP scores expressed in mean ± SD.

TABLE II. Risk of Leukemic Transformation With Myelosuppressive Therapy*

Therapy	Polycythemia vera	Polycythemia vera, myeloid metaplasia with myelofibrosis, and essential thrombocytosis
No. treatment or aspirin	—	0/11
Phlebotomy	2/18	2/18
Hydroxyurea	1/16	2/25
^{32}P	0/2	0/2
Alkylating agent	—	0/1
More than 1 myelosuppressive agent	1/4	1/5
Interferon-α	0/2	0/2

*There is no difference in the risk of leukemic transformation by treatment ($P = 0.5$).

2), and the total dose of melphalan was 20 mg/month for 6 years. The patients were followed for a median duration of 5.2 years, with a range of 4 months to 20 years.

Five of the 64 patients in this cohort transformed into MDS/AL. The breakdown according to the treatment is as follows: 0 out of 11 who received no treatment or aspirin, 2 out of 18 treated with phlebotomy alone, 2 out of 25 who received HU, and 1 who received more than one myelosuppressive agent (Table II). None of the patients who were treated with p32, melphalan, and IFN-α progressed to MDS/AL, but their numbers are small. There was no difference in the risk of transformation to MDS/AL based on the treatment received ($P = 0.56$). In particular, there was no evidence of an association between HU use and transformation to MDS/AL. The duration of myelotoxic therapy before transformation to MDS/AL was 18 months, 48 months, and 98 months. Three of 5 patients who transformed have died.

DISCUSSION

The leukemogenic potential of myelosuppressive therapy in PV remains a controversial subject. The natural

[18,19]. In some studies, the survival of PV pa phlebotomy parallels that of general populatio suppressive agents, however, become necessa than one-half of patients to prevent significant in the form of thromboembolic complications rhage. During the 1950s and 1960s, p32 and therapy were used extensively to treat PV. In a 1,222 patients collected from different institu Modan and Lilienfeld [20] reported an incidenc leukemia in 11% of patients treated with p32 an versus 1% in those treated without these mo 1981, the PVSG reported on their prospective ized trial of phlebotomy alone versus p32 versu bucil as treatment of PV [4]. The study showe risk of leukemic transformation with chloram 13 times that of phlebotomy, and 2.3 times t p32 arm. This alarming finding led to disconti the chlorambucil arm. Subsequent follow-up showed that at 10 years, the risk of leukemic tr tion was similar in the chlorambucil and p3 13–14%, because AL in the p32-treated group appear predominantly between the 5th and 1

The findings of the European Organization fo

or busulfan developed AL. The difference between the American and European findings may be due to different dose schedules.

Since 1981, HU has become the main myelosuppressive agent in the management of PV and has been considered the drug of choice by PVSG investigators [5]. It suppresses DNA synthesis by inhibiting ribonucleotide reductase. Despite its use for more than 20 years, its leukemogenic potential remains unknown. The PVSG has treated 51 patients with HU, 3 (5.9%) of whom developed AL. When compared with historical controls, this risk was not found to be statistically significant. Other studies suggest a leukemogenic risk of about 1% with HU [6–8].

HU also remains one of the major drugs in the management of chronic granulocytic leukemia (CGL) and other myeloproliferative disorders [14,15,22,23]. Recent studies show that it may prolong survival in CGL and prevent thrombotic complications in patients with ET [22,23]. There appears to be no increased risk of transformation to AL in these patients. The expanding list of indications for HU now includes sickle cell disease. In the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, 299 patients were enrolled between 1992 and 1994 [24]. The starting dose was 15 mg/kg, and the mean follow-up is 21 months. Although the follow-up is short, no malignant disorders have been seen in these patients.

We undertook this analysis to expand further on the leukemogenic risk of HU in PV. In an earlier study [25], we showed that the use of HU alone did not present risk of leukemic transformation, but the use of multiple myelotoxic agents was associated with a significant increase in this risk. This study includes a larger number of patients. Our data do not show any association between HU use and increase in the risk of leukemic transformation. We have also analyzed data on patients with ET and MMM, as these disorders are also treated frequently with HU. Addition of these patients also did not alter the estimated risk of leukemic transformation (2 out of 25 or 8%, Table II). However, this sample of 25 patients is insufficient for providing conclusive results. Based on a 5% type 1 error, and our limited sample size, the true rate could be higher.

With its widening spectrum of clinical indications, concerns about the mutagenic effects of HU remain valid. It is being used extensively in chronic myeloproliferative disorders, and more recently in sickle cell anemia, where the bone marrow is proliferating constantly because of the hemolytic process. Will this agent be safe in the long run? To answer this question in chronic myeloproliferative disorders, randomized studies involving hundreds of patients will need to be undertaken. That does not appear feasible in the current environment. We believe that our data contribute additional useful information to this area.

In summary, the use of hydroxyurea for the treatment of polycythemia vera, myeloid metaplasia with myelofibrosis, and essential thrombocytosis does not appear to be associated with increased risk of leukemic transformation. Larger randomized studies will be necessary to confirm these findings.

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